Background
Andexanet alfa is the first FDA-approved reversal agent for life-threatening or bleeding associated with factor Xa inhibitors1. Limited studies assessing efficacy of four-factor prothrombin complex concentrate (4F-PCC) for treatment of factor Xa inhibitor-associated major bleeding2;3;4. Comparative studies of andexanet alfa vs 4F-PCC are limited4.

Purpose
To assess the efficacy and safety of andexanet alfa vs 4F-PCC for reversal of factor Xa inhibitors in the setting of intracranial hemorrhage (ICH)

Methods
Single-center, IRB approved, matched cohort study
Andexanet alfa patients matched with 4F-PCC patients (age and ICH type)
4F-PCC patients were selected from June 2013 to June 2018
Andexanet alfa patients were selected from June 2018 to February 2020
Bivariate analysis and multivariate logistic regression (interim analysis)

Primary Outcome Measure
Percentage of patients achieving excellent/good hemostatic efficacy on repeat head CT
• Hemostatic efficacy classified based on Sarode and colleagues criteria5
• Repeat CT's qualitatively described as stable/improved classified as excellent/good
• Repeat CT's described as worse were sent to neuro-radiologist for volume measurement

Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>4F-PCC (n = 31)</th>
<th>Andexanet alfa (n = 31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median [IQR]</td>
<td>86 (75.8-89.0)</td>
<td>84 (78-90)</td>
<td>0.746</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>20 (64.5)</td>
<td>18 (58.1)</td>
<td>0.602</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>15 (14-15)</td>
<td>14 (14-15)</td>
<td>0.503</td>
</tr>
<tr>
<td>Baseline GCS, median [IQR]</td>
<td>5 (16.1)</td>
<td>2 (6.5)</td>
<td>0.229</td>
</tr>
<tr>
<td>SBP at baseline in mmHg, mean (SD)</td>
<td>153 (25)</td>
<td>153 (33)</td>
<td>0.962</td>
</tr>
<tr>
<td>Stroke, no. (%)</td>
<td>5 (16.1)</td>
<td>11 (35.5)</td>
<td>0.082</td>
</tr>
<tr>
<td>Xa Inhibitor, no. (%)</td>
<td>20 (64.5)</td>
<td>22 (71.0)</td>
<td>0.503</td>
</tr>
<tr>
<td>Apixaban</td>
<td>9 (29.0)</td>
<td>10 (32.3)</td>
<td>0.313</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0 (0)</td>
<td>1 (3.2)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Time from first dose of Xa Inhibitor, no. (%)
6 hours or less | 23 (74.2) | 28 (90.3) | 0.965 |
Concomitant antiplatelet use, no. (%) | 9 (29.0) | 12 (38.7) | 0.421 |
Spontaneous Bleed, no. (%) | 19 (61.3) | 15 (48.4) | 0.307 |
Type of ICH, no. (%) | 11/14 | 16/16 | 0.793 |
Intracerebral Hematoma 1P1H/VH | 16 (51.6) | 16 (51.6) | 1 |
Hematoma Volume (mL), median [IQR] | 10.6 [2.0-27.1] | 6.7 [1.8-18.8] | 0.497 |
Subdural Hematoma | 13 (41.9) | 13 (41.9) | 1 |
Hematoma Thickness (mm), median [IQR] | 8 [7-11] | 10 [5-14] | 0.644 |
Subarachnoid Hemorrhage | 2 (6.5) | 2 (6.5) | 1 |
Hematoma Depth (mm) | 10 (5-13) | 11 (5-15) | 0.962 |

Bleed size and at or above median, no. (%) | 15 (51.7%) | 14 (48.3%) | 0.793 |
Excluded 2 subarachnoid hemorrhages in each group due to inability to quantify bleed volume

Results

Primary Outcome (Bivariate Analysis)
Excellent/good hemostatic efficacy | 22 (71.0) | 28 (90.3) | 0.054 |
Secondary Outcomes (Bivariate Analysis)
ER arrival to treatment administration (hrs), median [IQR] | 1.37 [0.99-3.24] | 1.53 [1.16-2.97] | 0.683 |
In-hospital mortality, no. (%) | 3 (9.7) | 2 (6.5) | 0.451 |

Discussion
Andexanet alfa had a 19.3% higher rate of excellent/good hemostatic efficacy compared to 4F-PCC
Baseline GCS score had greatest impact on hemostatic efficacy
No differences in secondary outcomes observed
One andexanet alfa patient developed bilateral PE during index hospitalization
ER arrival to treatment administration times are similar in both groups. Andexanet alfa median time of 1.53 hrs is lower than reported in other studies (4.7 hrs ANNEXA-4 and 3.6 hrs Barra et al)
Interim observations encouraging however, full goal enrollment of 120 patients in each group to meet power. Efficacy cannot be determined until power met

Limitations:
• Retrospective, observational study design, small sample size
• Limited patient follow-up

Disclosure
Authors of this presentation have the following to disclose concerning possible personal or financial relationships with commercial entities that may have a direct or indirect interest in the subject matter of the presentation:
John D'Arcangelis, Amy Giovino, Eileen Shomo, Andre McMahon, Bren Magruder: Nothing to disclose.
Mauro Concha: Primary investigator for Andexanet-4 study, speaker and consultant for Portola.

References

P1
Retrospective study of andexanet alfa vs 4-factor prothrombin complex concentrate for reversal of factor Xa inhibitors in the setting of intracranial hemorrhage
John D’Arcangelis, PharmD, Eileen Shomo, PharmD, Andre McMahon, PharmD, Bren Magruder, PharmD, Mauricio Concha, MD, Amarisio Giovinno, PharmD
FDA = Food and Drug Administration; 4F-PCC = Four factor prothrombin complex concentrate; IHB = Investigational Review Board; CT = computer tomography; GCS = Glasgow Coma Scale; SBP = Systolic blood pressure; ICH = intracerebral hemorrhage; ALF = Assisted living facility; SNF = Skilled nursing facility; TE = Thrombotic Embolism

Discussions:
• Andexanet alfa had a 19.3% higher rate of excellent/good hemostatic efficacy compared to 4F-PCC
• Baseline GCS score had greatest impact on hemostatic efficacy
• No differences in secondary outcomes observed

Limitations:
• Retrospective, observational study design, small sample size
• Limited patient follow-up
• Time to repeat CT varied

References: